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Eosinophilic Esophagitis
A Review

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IMPORTANCE Eosinophilic esophagitis (EoE) is a chronic immune-mediated inflammatory disease of the esophagus that affects an estimated 34.4/100 000 people in Europe and North America. EoE affects both children and adults, and causes dysphagia, food impaction of the esophagus, and esophageal strictures.

OBSERVATIONS EoE is defined by symptoms of esophageal dysfunction, such as vomiting, dysphagia, or feeding difficulties, in a patient with an esophageal biopsy demonstrating at least 15 eosinophils per high-power field in the absence of other conditions associated with esophageal eosinophilia such as gastroesophageal reflux disease or achalasia. Genetic factors and environmental factors, such as exposure to antibiotics early in life, are associated with EoE. Current therapies include proton pump inhibitors; topical steroid preparations, such as fluticasone and budesonide; dietary therapy with amino acid formula or empirical food elimination; and endoscopic dilation. In a systematic review of observational studies that included 1051 patients with EoE, proton pump inhibitor therapy was associated with a histologic response, defined as less than 15 eosinophils per high-power field on endoscopic biopsy, in 41.7% of patients, while placebo was associated with a 13.3% response rate. In a systematic review of 8 randomized trials of 437 patients with EoE, topical corticosteroid treatment was associated with histologic remission in 64.9% of patients compared with 13.3% for placebo. Patients with esophageal narrowing may require dilation. Objective assessment of therapeutic response typically requires endoscopy with biopsy.

CONCLUSIONS AND RELEVANCE EoE has a prevalence of approximately 34.4/100 000 worldwide. Treatments consist of proton pump inhibitors, topical steroids, elemental diet, and empirical food elimination, with esophageal dilation reserved for patients with symptomatic esophageal narrowing.

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Supplemental content

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Eosinophilic esophagitis (EoE) is a chronic immune-mediated inflammatory condition of the esophagus. The incidence of EoE is approximately 7.7/100 000 per year in adults, and EoE affects an estimated 34.4/100 000 people in Europe and North America.[1,2] This review summarizes current evidence regarding the diagnosis and treatment of EoE.

Methods/Literature Search

A literature search was performed in PubMed for the period between January 1, 2010, and May 13, 2021, by a clinical librarian. Key terms included *eosinophilic esophagitis*, *therapy*, *diagnosis*, *epidemiology*, *randomized clinical trials*, and *umbrella reviews*. Controlled vocabulary and keywords associated with each term were examined and combined using Boolean logic. The search syntax can be found in the eAppendix in the Supplement. Of 323 articles retrieved, 6 systematic reviews and meta-analyses, 8 clinical trials, and 5 observational studies were included in this review.

Diagnosis of Eosinophilic Esophagitis

Based on the 2018 AGREE (A Working Group on PPI-REE) international consensus conference, EoE is defined by symptoms of esophageal dysfunction, such as vomiting, dysphagia, or feeding difficulties, in a patient with esophageal biopsies demonstrating at least 15 eosinophils per high-power field (HPF) in the absence of other conditions associated with esophageal eosinophilia such as gastroesophageal reflux disease, achalasia, vasculitis, hypereosinophilic syndrome, Crohn disease, Ehlers-Danlos syndrome, graft-vs-host disease, infections, and drug hypersensitivity (**Box 1**).[3] A trial of a proton pump inhibitor (PPI) to exclude a diagnosis of gastroesophageal reflux disease is no longer considered appropriate in diagnosing EoE.[3]

Epidemiology

In a meta-analysis of 18 population-based studies, the pooled incidence of EoE was 7.7/100 000 per year in adults.[2] The prevalence

varied by country and continent. The most recent pooled prevalence data demonstrated 34.4 cases/100 000 inhabitants and 42.2/100 000 among adults.[2] The incidence of EoE is increasing, perhaps due to increasing awareness of EoE along with increased rates of biopsy sampling of the esophagus during esophogastroduodenoscopy. However, additional evidence suggests an overall increase in the incidence of EoE even after taking into account increased disease awareness, a phenomenon also observed for other atopic diseases.[4]

Pathophysiology

The pathophysiology of EoE is incompletely understood (**Figure 1**). In susceptible individuals, exposure to foods that are ubiquitous in the diet, such as milk and wheat, is associated with infiltration of the esophageal mucosa with a mixed granulocyte population (eosinophils, mast cells, and basophils).[5,6] This inflammation diminishes epithelial barrier integrity and damages the mucosa.

Genetics and Environment

EoE is more common among first-degree relatives of patients with EoE, who have a higher risk of developing EoE than the general population.[7] Genome-wide array studies have identified 31 candidate genes, including *TSLP*, *CAPN14*, and *EMSY*,[8-11] that are associated with EoE. In addition to these genetic risk factors, unknown environmental factors, especially in early life, are associated with development of EoE. In twin studies, the frequency of EoE in a monozygotic twin of a patient with EoE was 41% and 24% in a dizygotic twin of a patient with EoE.[7] The risk of EoE is approximately 2.4% in siblings with the disease, suggesting a perinatal shared environmental risk factor beyond genetics.[7] In 4 of 5 observational studies that evaluated early-life exposures associated with EoE, antibiotic exposure during infancy was associated with increased risk for development of EoE.[12] Whether the microbiota of the esophagus contribute to disease pathogenesis remains unclear.[13]

Clinical Presentation

The clinical presentation of EoE varies depending on age at presentation. Infants and young children are more likely to present with nonspecific symptoms or signs such as failure to thrive, feeding difficulties, and vomiting (**Box 2**). Adolescents and adults typically have symptoms associated with esophageal fibrosis, with more than 70% of adults presenting with dysphagia and 30% presenting with food impactions.[14] Approximately 50% of patients who present on an emergency basis with an esophageal food impaction requiring endoscopic removal have EoE.[15,16] In patients with EoE, longer periods of untreated inflammation are associated with a higher prevalence of esophageal fibrosis, dysphagia, and food impaction.[17] A cohort study of 721 patients with EoE from the Netherlands reported that in patients with symptoms of EoE for more than 21 years at the time of diagnosis, the proportions of patients with strictures and esophageal food impactions were 52% and 57%, respectively. For patients with symptom duration of less than 2 years at the time of diagnosis, the proportions were 19% and 24%, respectively. It was estimated that for each year of untreated EoE symptoms, the risk of stricture increased by 9% (odds ratio, 1.09 [95% CI, 1.05-1.13]).[18]

Patients with EoE typically modify their eating behavior by chewing thoroughly, selecting softer foods, and drinking frequently during meals. These behaviors may contribute to a delay in diagnosis. Adults with EoE are typically diagnosed a mean of 7 years after symptom onset.[17]

Box 1. Diagnostic Criteria for Eosinophilic Esophagitis

Symptoms of esophageal dysfunction
- Dysphagia
- Food impaction
- Food refusal
- Heartburn
- Regurgitation
- Vomiting
- Chest pain

Endoscopic biopsies with >15 eosinophils per high-power field

Exclusion of other causes of esophageal eosinophilia such as
- Gastroesophageal reflux disease
- Eosinophilic gastrointestinal disease
- Achalasia
- Hypereosinophilic syndrome
- Connective tissue diseases
- Crohn disease
- Infections
- Pill-induced esophagitis
- Graft-vs-host disease

Diagnosis and Assessment

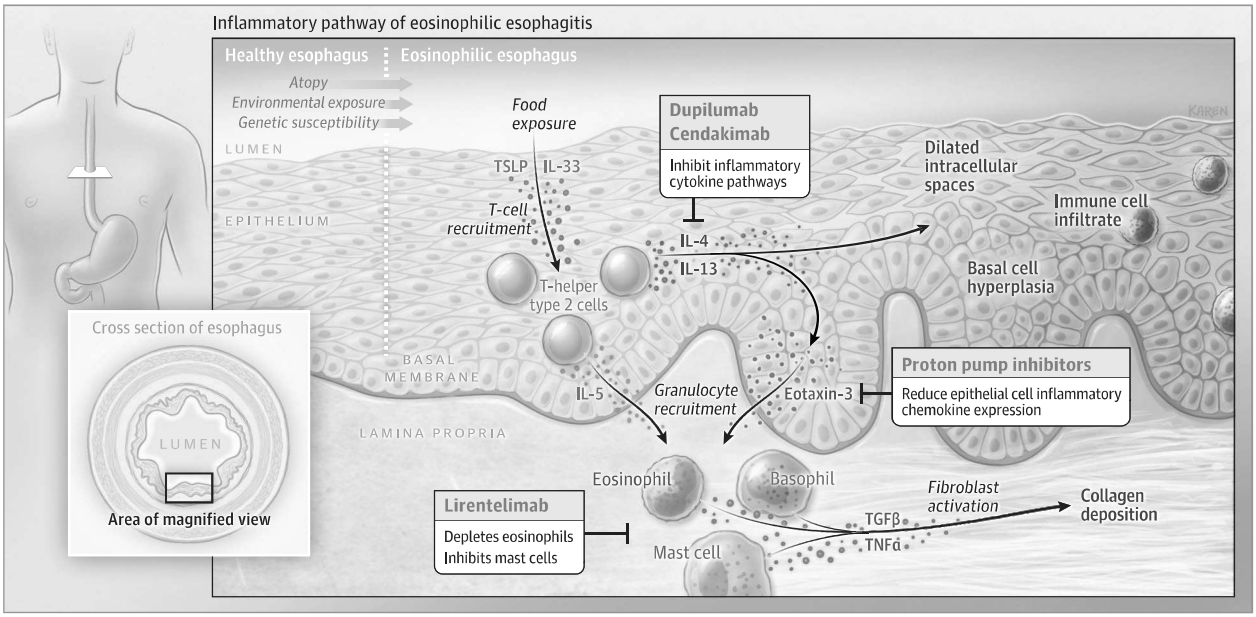
Endoscopy

Diagnosis of EoE requires endoscopy with biopsy. Endoscopic findings in patients with EoE consist of furrows (appearing as vertical lines within the mucosa), trachealization (appearing as concentric rings of esophageal narrowing), exudates (white plaques), edema (decreased vasculature of mucosa), and stricture (**Figure 2**).[19] The American College of Gastroenterology's evidence-based approach to diagnosis and management of EoE recommends obtaining a minimum of 6 biopsies (including both proximal and distal esophagus) from any patient who may have EoE. In approximately 10% to 25% of patients with EoE, the esophagus may have a normal appearance on endoscopy.[20]

Pathology

Even in the setting of visual findings on endoscopy, the gold standard of EoE diagnosis is histology. Currently, 15 eosinophils or more per HPF in the maximally affected high-power field is required for diagnosis.[3] This threshold value has been shown to be 100% sensitive and 96% specific for diagnosis.[21] The goal of therapy is to improve symptoms and reduce the eosinophil count below 15 eosinophils per HPF.

Figure 1. Pathophysiology of Eosinophilic Esophagitis



Early-life exposures, genetic factors, and an atopic state likely increase disease susceptibility in eosinophilic esophagitis. Exposure to antigens causes the esophageal epithelium to release alarmins, IL-33, and thymic stromal lymphopoietin (TSLP). These cytokines in turn stimulate T-helper type 2 (Th2) cells' secretion of IL-13, IL-4, and IL-5. IL-13 and IL-4 stimulate the changes seen in the esophageal epithelium, including basal cell hyperplasia and dilated intracellular spaces. Chemotaxins, eotaxin-3 and IL-5, lead to granulocyte infiltration. The mixed cytokine milieu also contributes to the activation of fibroblasts in the lamina propria, collagen deposition, and tissue stiffness.

Box 2. Frequently Asked Questions

What Are the Most Frequent Presenting Symptoms in EoE?
The most frequent symptoms in adults and adolescents are dysphagia and food impactions. In children, vomiting, weight loss, and heartburn are more common.

How Is the Diagnosis of EoE Typically Made?
EoE is diagnosed by endoscopy with biopsy of the esophagus showing >15 eosinophils per high-power field.

What Is the Natural History of EoE?
Over time, untreated EoE can lead to esophageal fibrosis and stricture in patients.

What Is First-line Therapy for EoE?
There is no accepted first-line therapy for EoE and no therapy is 100% effective. Shared decision-making examining risks and benefits of an elimination diet, proton pump inhibitors, topical steroids, dilation, or enrollment into clinical trials should be offered to patients with EoE.

Abbreviation: EoE, eosinophilic esophagitis.

New and Emerging Diagnostic Methods

Symptoms of feeding difficulties and dysphagia are not reliable indicators of continued EoE disease activity, and resolution of symptoms is not a reliable indicator of remission.[22] While no clinical trials have demonstrated that serial endoscopy tests in patients with EoE improve outcomes, follow-up endoscopy is typically recommended for patients after therapy initiation for EoE to document histologic remission. In addition, it is essential to ensure remission is maintained, because active esophageal inflammation is associated with fibrostenosis and stricture.[17] In a retrospective study of 200 adults with EoE, a longer duration of untreated EoE was associated with a higher prevalence of fibrosis.[17] Patients with less than 2 years of untreated disease had a 17.2% stricture prevalence, those with a 5- to 8-year delay in treatment had a 38.9% stricture prevalence, and those with a delay in treatment exceeding 20 years had a 70.8% stricture prevalence.[17] New noninvasive technologies are under study to measure disease activity without the need for sedated endoscopy.

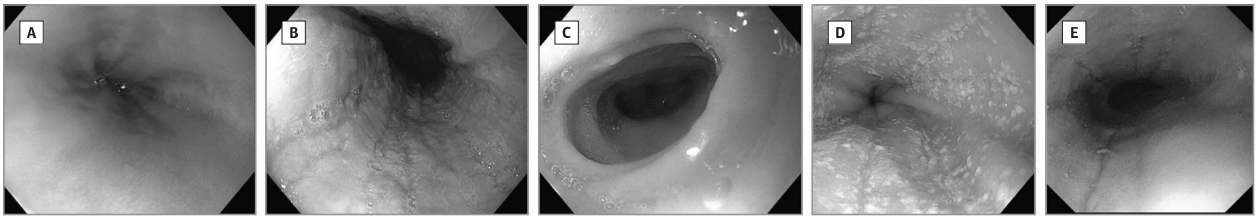
Noninvasive Methodologies to Determine Disease Activity

A noninvasive approach to assess disease activity involves use of a capsule containing a mesh sponge with a string attached. The capsule is swallowed while the patient holds the string outside of the mouth. Once the capsule dissolves, the mesh sponge expands and is removed by pulling the string through the mouth. Esophageal scrapings are collected in the mesh matrix and formalin fixed for histologic analysis. A multicenter proof-of-principle study demonstrated that 102 of 105 patients had adequate tissue isolated from the sponge for analysis with a sensitivity of 75% and specificity of 86% for determining disease activity, defined by eosinophil count on biopsy.[23]

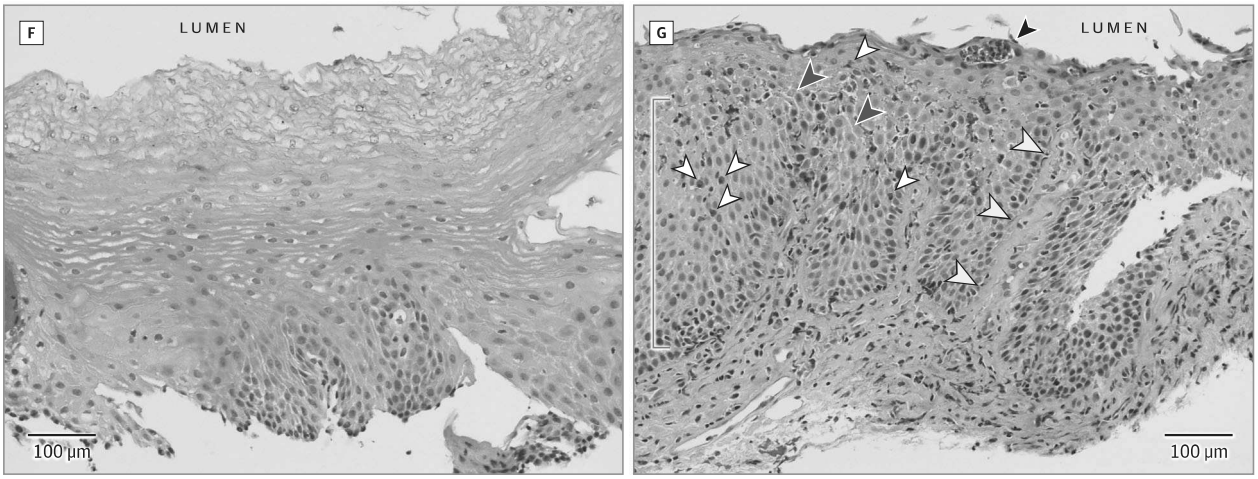
The esophageal string test uses a capsule with an absorptive string that unravels in the esophagus while the patient holds the string outside of the mouth. The string stays in place for 1 hour and is then pulled out of the mouth. Unlike the capsule containing a mesh sponge with a string attached that collects esophageal tissue,

Figure 2. Endoscopic and Histologic Appearance of the Eosinophilic Esophagitis (EoE) Esophagus

Endoscopic appearance of normal esophagus tissue and eosinophilic esophagitis



Histologic appearance of normal esophagus tissue and eosinophilic esophagitis



Endoscopy of EoE: normal esophagus (A); linear furrows (B); mucosal pallor representing edema, decreased vascular pattern, and concentric rings or trachealization (C); small white plaques (D); and esophageal narrowing and rent due to endoscope passage (E). Histology (hematoxylin and eosin) of EoE: F, Normal esophageal squamous epithelium with inconspicuous basal layer, luminal squamous differentiation, and absence of inflammation. G, EoE mucosa demonstrating elongated papilla (yellow arrowheads), basal cell hyperplasia (blue line), infiltrating eosinophils (white arrowheads), eosinophil microabscess (black arrowhead), and epithelial spongiosis (pink arrowheads). Images courtesy of Benjamin Wilkins, MD, PhD, Children's Hospital of Philadelphia.

the string absorbs esophageal secretions. In a study involving 134 patients, analysis of eosinophil granule proteins and cytokines on the string was 80% sensitive and 75% specific for determining EoE disease activity, defined by eosinophil count on biopsy.[24]

Transnasal endoscopy should be performed without sedation and consists of passing a thin endoscope through the nares into the esophagus where biopsies are obtained. This procedure can be performed in children as young as 6 years of age, and may be facilitated with the aid of virtual reality goggles to help distract children from the ongoing procedure.[25]

Approaches to Assess Esophageal Function

Determining which patients will have a narrow-caliber esophagus or a fibrostenotic phenotype esophagus is possible with genetic testing or use of more invasive techniques. A 96-gene quantitative polymerase chain reaction panel has been developed that can distinguish patients with EoE from controls.[26,27] In an investigation that included 185 patients in the discovery cohort and 100 patients in the validation cohort, patients evaluated with this panel were classified as having either fibrostenotic (risk ratio [RR], 7.98 [95% CI, 1.84-34.64]; $P = .001$) or inflammatory and steroid-refractory EoE (RR, 2.77 [95% CI, 1.11-6.95]; $P = .04$) based on gene expression in the tissue (absolute rates not provided).[27]

The functional luminal imaging probe (FLIP) is a US Food and Drug Administration (FDA)–approved measuring tool that can be used during sedated upper endoscopy. FLIP is a balloon that is inflated in the esophagus that measures pressure and diameter along 16 cm of the esophagus to determine esophageal distensibility and compliance.[28-30] FLIP measurements in children and adults demonstrated that patients with a history of food impactions have decreased distensibility compared with those without complications. Specifically, the distensibility plateau of those with food impactions (n = 19) was 113 mm^2 compared with 229 mm^2 in those without these complications (n = 30).[31]

Therapy

There are no FDA-approved treatments for EoE. Currently available treatments are listed in the Table. Therapies should be selected based on efficacy, ease of administration, cost, and patient preference. A shared decision-making model with patients that reviews benefits and drawbacks of each option is recommended.[37]

Table. Current Treatment Options for Eosinophilic Esophagitis

Treatment approach	Dose or methods	Pooled histologic response	Adverse effects	Other considerations
Proton pump inhibitors[a]	Omeprazole or equivalent, 20 mg, twice daily Pantoprazole, 40 mg, twice daily Lansoprazole, 30 mg, twice daily Rabeprazole, 20 mg, twice daily	41.7% in a systematic review of observational data of 1051 participants compared with a historical placebo comparison group of 13.3%[32]	Acute: Headache <5%[33] Diarrhea <5%[33] Enteric infections (1.4% in 53 152 patient-years of follow-up)[34] Proposed chronic[35]: Chronic kidney disease (0.1%-0.3%/patient/y) Bone fracture (0.1%-0.5%/patient/y) Dementia (0.07%-1.5%/patient/y)	Low cost Readily available Ease of administration Well tolerated
Topical corticosteroids	Fluticasone, 440-880 µg, twice daily Budesonide, 1-2 mg, twice daily	64.9% in 8 randomized clinical trials of 437 patients compared with 13.3% treated with placebo[32]	Esophageal candida (12%-16%) Oral thrush (2%-3%)[36]	Off-label use of asthma medications results in need to repurpose as slurry for budesonide and swallow instead of inhale for fluticasone Cost may be considerable because it is not always covered by insurance
Elemental diet	Consists of diet exclusively made up of amino acid–based formula	93.6% in 6 observational studies of 431 patients vs 13.3% in a historical placebo comparison group[32]	No adverse effects	Cost Palatability is poor After elemental diet, reintroduction of food groups may increase IgE-mediated allergies
6-Food elimination diet	Eliminated foods consist of eliminating milk, wheat, soy, egg, nuts, and fish/seafood	67.9% in a systematic review of 633 patients in 9 observational studies compared with 13.3% response in a historical placebo comparison group[32]		Dairy and wheat are the most commonly implicated food groups Requires multiple endoscopies to identify culprit food group(s) Requires well-motivated patient

[a] Only the enteric infections have been associated in randomized clinical trials.[33,34]

Dietary Elimination

Because EoE is a non–IgE-mediated allergic disease, attempting to eliminate the allergens may result in disease remission in some patients. There are 3 approaches to dietary therapy: an elemental diet (exclusively drinking a formula without any intact protein, ie, amino acid–based formulas), empirical food elimination, and allergy test–directed food elimination. An elemental diet consists of a liquid form of nutrition composed of amino acids, fats, sugars, vitamins, and nutrients that is readily assimilated and absorbed. A recent systematic review of 6 single-group observational studies with 431 patients reported that an elemental diet was associated with histologic remission (<15 eosinophils per HPF) in 93.6% of patients compared with 13.3% in a historical placebo comparison group from clinical trials of topical corticosteroid (807 fewer cases per 1000 in the historical placebo group) (RR, 0.07 [95% CI, 0.05-0.12]).[32] However, this approach is costly, inconvenient, and associated with undesirable taste. In addition, it can be difficult to ingest sufficient formula to maintain body weight, and some patients require a feeding tube due to palatability problems from the formula. After elemental diet nutrition, reintroduction of food groups may be associated with de novo development of IgE-mediated food allergies. Therefore, this approach is best used in collaboration with an allergist to assist with food reintroduction to avoid acute allergic reaction.[38]

Empirical elimination of food groups commonly implicated in EoE is another dietary approach. The most common approach is elimination of the 6 most common food groups associated with EoE: milk, wheat, eggs, soy, peanuts/tree nuts, and fish/shellfish.[39] A recent systematic review of 9 single-group observational studies with a total of 633 patients with EoE found that dietary elimination was associated with a histologic response in 67.9% of patients (<15 eosinophils per HPF) compared with 13.3% in a historical placebo comparison group (RR, 0.38 [95% CI, 0.32-0.43]).[32] Dairy, wheat, and eggs are the most commonly implicated food groups. In patients who respond, foods can be reintroduced sequentially. A practical approach to food reintroduction is to start with fish/seafood and peanuts/tree nuts followed by endoscopy after 6 weeks. Patients who attain a response, defined as less than 15 eosinophils per HPF, may add dietary soy and eggs. If another repeat endoscopy after 6 weeks demonstrates continued response, wheat may be introduced, followed by repeat endoscopy to assess response, dairy introduction, and repeat endoscopy.[39,40] The repeat endoscopies, dietary adherence, and long-term dietary restrictions can be challenging for patients. Therefore, several less-restrictive approaches have been studied. Pooled histologic response from a limited number of single-group observational studies for 4-food (milk, wheat, eggs, and legumes) (3 single-group studies, n = 426), 2-food (milk and wheat) (2 single-group studies, n = 311), and 1-food (milk) (2 group studies, n = 203) elimination diets were 56.9%, 42.1%, and 54.1%, respectively.[32] These approaches involve fewer endoscopies and better convenience for patients. The decision to follow a stepdown approach by starting with a 6-food elimination diet or a stepup approach by starting with either a 1-, 2-, or 4-food elimination diet is best handled by shared decision-making with the patient.

Another dietary approach is to use allergy testing to detect potential food triggers, using results to prescribe dietary elimination. However, EoE is not an IgE-mediated disease and allergy

testing (prick testing, serum IgE testing, and patch testing) is not standardized for non–IgE-mediated disease. A systematic review of 11 single-group studies with 830 patients reported that allergy-directed elimination diet was associated with a response rate of 50.8% compared with 13.3% in a historical placebo comparison group (RR, 0.57 [95% CI, 0.33-0.73]).[32]

Proton Pump Inhibitors

Until 2018, an endoscopy with biopsy showing more than 15 eosinophils per HPF after an 8-week trial of high-dose PPIs (ie, omeprazole, 40 mg, daily) was considered standard care to exclude esophageal inflammation due to gastroesophageal reflux disease and an entity known as PPI responsive esophageal eosinophilia (PPI-REE), in which patients had symptoms of esophageal dysfunction and more than 15 eosinophils per HPF, with improvement of both in response to high-dose PPI therapy. However, an updated diagnostic algorithm in 2018 eliminated the requirement of a PPI trial as a diagnostic requirement, and instead classified PPIs as a treatment option for patients with EoE.[3] This change was based on studies demonstrating that the clinical, endoscopic, histologic, and molecular characteristics of PPI-REE and EoE were similar[41-43] and there was no difference between PPI-REE and EoE. In EoE, PPIs may have anti-inflammatory effects independent of gastric acid suppression: antioxidant properties, inhibition of immune cell function, and reduction of epithelial cell inflammatory cytokine expression.[42,44,45]

A systematic review of 23 observational studies with 1051 patients with EoE reported that PPI therapy was associated with a histologic response in 41.7% of patients (defined as <15 eosinophils per HPF) compared with 13.3% in the historical placebo group (RR, 0.66 [95% CI, 0.61-0.72]).[32] An earlier systematic review and meta-analysis of 33 studies (including 11 prospective observational studies, 2 randomized clinical trials, case reports, and retrospective studies) comprising 619 patients reported symptomatic improvement in 60.8% (95% CI, 48.4%-72.2%) of patients treated with PPIs, but heterogeneity in these analyses was considerable (I^2 = 80.2%).[46]

PPIs are a reasonable first-line therapy for EoE given their low cost, tolerability, generally favorable safety profile, and ease of administration. There does not seem to be a difference in efficacy between different PPIs or between administration once daily vs twice daily.[41] However, PPIs may be less effective in patients who have failed to respond to topical corticosteroids or dietary therapy as well as in patients with a fibrostenotic phenotype.[47]

Potential harms of long-term PPI therapy include associations of PPIs with pneumonia, dementia, myocardial infraction, chronic kidney disease, fracture, enteric infections, small bowel bacterial overgrowth, *Clostridioides difficile*–associated infection, and micronutrient deficiency anemia.[35] However, evidence is inadequate to establish any causal relationship between PPIs and these potential harms, and many of the effect sizes are small (absolute risk increased from 0.3% to 1.5% per patient per year).[48] A 3-year randomized clinical trial that assessed the safety of PPIs among 17 598 participants with stable cardiovascular disease and peripheral artery disease receiving rivaroxaban or aspirin reported no difference in safety events with the exception of enteric infections between the PPI and placebo groups (1.4% vs 1.0%; odds ratio, 1.33 [95% CI, 1.01-1.75]).[34]

Swallowed Topical Steroids to Treat EoE

Swallowed corticosteroids are the mainstay of therapy of EoE; however, no formulations are approved yet by the FDA for EoE treatment. A recent double-blind clinical trial by Dellon et al[36] randomized 111 adults with a new diagnosis of EoE to either fluticasone, 880 µg, swallowed twice daily from a multidose inhaler or oral viscous budesonide, 1 mg, twice daily for 8 weeks. Peak eosinophil counts declined from 73 to 15 eosinophils per HPF in the budesonide group and from 77 to 21 eosinophils per HPF in the fluticasone group (P = .31). Histologic remission (<15 eosinophils per HPF) occurred in 71% of the budesonide and 64% of the fluticasone patients (P = .38) and change in symptoms, as measured by the dysphagia symptom questionnaire, was no different between either budesonide or fluticasone participants (mean [SD], −5.8 [9.6] vs −4.0 [8.3]; P = .37). However, this randomized trial was limited by the lack of a placebo comparator.

A recent systematic review of 8 double-blind placebo-controlled clinical trials of topical corticosteroid treatment that included 437 patients for a mean of 8 weeks reported that topical corticosteroids were associated with histologic remission in 64.9% of patients (<15 eosinophils per HPF) (risk difference, 537/1000) compared with 13.3% in patients treated with placebo (RR , 0.39 [95% CI, 0.85-1.19]).[32] Clinical trials have evaluated initial treatment duration of 2 to 12 weeks. In a randomized clinical trial of 88 adults, budesonide orodispersible tablets (1 mg twice daily) attained both clinical and histologic remission in 57.6% of patients at 6 weeks and 84.7% at 12 weeks.[49] This suggests that optimal initial duration of topical steroid therapy is at least approximately 12 weeks.

Topical corticosteroids are well tolerated, and the most common adverse effects with short-term treatment with topical corticosteroids is asymptomatic esophageal *Candida* infection, which occurred in 12% to 15% of patients in the randomized clinical trial described above.[36] In a systematic review of 7 randomized clinical trials of 367 patients, there was no association of topical steroid use with adrenal insufficiency compared with placebo.[50] However, in a recently published clinical trial of 318 patients randomized to a higher dose of budesonide suspension (2 mg twice daily) or placebo administered for 8 weeks, adrenal suppression was encountered in 1.4% and adrenal insufficiency in 0.9% of the budesonide group compared with no such events in the placebo group.[51] Current evidence suggests that swallowed steroids for topical treatment of the esophagus are safe, with minimal systemic absorption.[38]

Efforts to develop esophageal-specific corticosteroid preparations are ongoing. The European Medicines Agency has approved budesonide orodispersible tablets.[49] A premixed oral budesonide oral suspension has been evaluated in a phase 3 clinical trial of 318 patients randomized to either budesonide oral suspension, 2 mg, or placebo twice daily. Both the histologic (53.1% vs 1.0%, P < .001) and symptom responses (52.6% vs 39.1%, P = .02) were greater in the budesonide group compared with placebo.[51]

Dilation

Endoscopic dilation is a therapeutic option for treating esophageal strictures, rings, and narrow-caliber esophagus in patients with EoE.

A systematic review and meta-analysis of 27 studies (1 randomized clinical trial, 18 cohort studies, 2 case series, and 6 case reports) including 845 patients found that dilation was associated with clinical improvement in 95% of patients with EoE (95% CI, 90%-98%), with a median duration of improvement of 12 months (range, 1 week-36 months).[52] Despite early concerns about increased perforation rates with dilation, esophageal dilation is generally safe. A systematic review and meta-analysis of 37 studies (1 randomized clinical trial, 25 cohort studies, 1 case-control study, and 10 case series or case reports) including 2034 dilations in 977 patients with EoE reported that dilation was associated with a perforation rate of 0.033% (95% CI, 0%-0.226%), bleeding rate of 0.028% (95% CI, 0%-0.217%), and hospitalization rate of 0.689% (95% CI, 0%-1.42%).[53] Chest discomfort was the most frequent adverse event, which occurred in 23.6% of patients (95% CI, 5.89%-41.3%).[52] However, dilation did not improve esophageal eosinophilic inflammation and ongoing mucosal damage.[54] This is important because histologic remission (<15 eosinophils per HPF) is associated both with a greater likelihood of improved esophageal diameter and a decreased need for subsequent dilation.[55]

Optimal timing of dilation in patients with EoE remains unclear. Ideally, inflammation should be controlled prior to initiating dilation. However, in the setting of medication nonadherence, strictures that do not respond to medical therapy, high-grade stenosis, or recurrent food impaction, esophageal dilation may be considered prior to control of inflammation.[56] The target goal of therapy should be an esophageal diameter of 15 to 18 mm.[20]

Combination Therapy

There are limited data on the effectiveness of multimodal therapy, consisting of topical steroids, PPIs, and dietary elimination.[57,58] One observational cohort study of 23 patients, of whom 21 were previously treated with topical corticosteroids or food elimination monotherapy, found global symptomatic improvement in 82% of patients.[58] However, the use of multiple therapies is associated with increased cost and adherence challenges. If multimodal therapy results in symptomatic and histologic remission, can be challenging to determine which treatment modality was effective. For patients with concomitant symptoms of reflux, such as heartburn and acid regurgitation, therapy with a histamine H2 antagonist or a PPI at the lowest dose (omeprazole, 20 mg, daily) to control symptoms is warranted. For patients who do not respond to any first-line therapies, consideration should be given to potential causes of ongoing symptoms including poor adherence, inadequate dosing of medications, inappropriate administration of topical steroids, or fibrostenosis.[57] Patients who do not respond to standard therapy should also consider enrolling in clinical trials testing new agents. It remains unknown whether multimodal therapy is effective for disease refractory to single-agent therapy.

Emerging Therapies: Biologics

A variety of monoclonal antibodies that either directly target eosinophils or inflammatory cytokine pathways, such as lirentelimab and dupilumab among others, are now undergoing clinical trials (NCT03633617, NCT04322708, NCT04543409, NCT04682639, NCT04753697). These compounds have the potential to treat EoE and concomitant atopic diseases and offer the convenience of less frequent dosing schedules. However, guidelines from the American Gastroenterological Association (AGA) and Joint Task Force on Allergy-Immunology (JTF) recommend that these therapies should only be considered in the context of a clinical trial.[38]

Maintenance Therapy

EoE is a chronic inflammatory disease. Observational studies suggest that untreated EoE is associated with disease progression characterized by strictures and esophageal narrowing as described above.[17,59] Furthermore, symptomatic, endoscopic, and histologic relapse, defined as more than 15 eosinophils per HPF, typically occur after therapy cessation. In the observation phase of the randomized clinical trial of fluticasone vs budesonide described above, 33 of 58 patients (57%) had symptom recurrence, with a median time to symptom recurrence of 244 days.[60] In an observational single-center study of 33 patients who had achieved clinical, endoscopic, and histologic remission, 27 (82%) had a relapse of EoE symptoms of dysphagia or chest pain at a median of 22.4 weeks (95% CI, 5.1-39.7) after cessation of swallowed topical steroids.[61] The AGA-JTF recommends continuation of topical steroids over discontinuation of therapy, based on a single trial of 28 patients that randomized patients to low-dose budesonide (0.25 mg twice daily) or placebo.[62] However, since the publication of the AGA-JTF recommendations, a 48-week European randomized clinical trial of maintenance therapy of budesonide orodispersible tablets in 204 patients reported that the primary combined end point of clinical and histologic remission (<15 eosinophils per HPF) occurred in 75%, 73.5%, and 4.4% of patients given 1 mg twice daily, 0.5 mg twice daily, and placebo, respectively.[63] Furthermore, median time to relapse in the placebo group was 87 days. The approach to maintenance therapy should involve shared decision-making, but rapid return of symptoms and prior complications, such as food bolus impaction, strictures, or narrow-caliber esophagus characterized by inability to pass an adult endoscope of 9-mm diameter, would favor maintenance therapy over no therapy.

Limitations

This review has several limitations. First, quality of evidence was not formally assessed. Second, some relevant references may have been missed. Third, natural history studies suggesting progression to esophageal narrowing are based on retrospective data. Fourth, other than for topical corticosteroid therapy, no randomized clinical trials evaluating other treatment modalities have been conducted.

Conclusions

EoE has a prevalence of approximately 34.4/100 000 people worldwide. Treatments consist of proton pump inhibitors, topical steroids, elemental diet, and empirical food elimination, with esophageal dilation reserved for patients with symptomatic esophageal narrowing.

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